## REMARKS

Claims 2-12, 17, 22-24 and 26-53 have been cancelled. Claims 1 and 18-20 have been amended. Claims 1, 13-16, 18-21 and 25 are now pending.

Applicants express their appreciation to Examiner McIntosh for conducting a telephone interview with Applicants on April 18, 2005. During the interview, Applicants distinguished the claimed sequential therapy as specified by amended claim 1 with the disclosure in the cited reference Bernacki et al. ("In Vitro Antitumor Activity of 9-Nitro-Camptothecin as a Single Agent and in Combination with other Antitumor Drugs," Annals of the New York Academy of Sciences, vol. 922, pp. 293-297, 2000).

In the Office Action, claims 1-16, 18-21, 23 and 25 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Bernacki et al. in view of the combination of Rubinfeld (U.S. Patent 6,191,119) and Achterrath (U.S. Patent No: 6,403,569).

Applicants cancel claims 2-12 and amend claims 1 and 18-20 to specify a method for treating cancer in a cancer patient with p53 mutation by using a sequential therapy of 9-nitro-20(S)-camptothecin (9NC) or 9-amino-20(S)-camptothecin (9AC) administered at least 1 day **after** administration of 5-fluorouracil (5-FU).

As discussed during the interview, Bernacki et al. neither teaches nor suggests the specific sequential therapy recited in claim 1, i.e., administration of 5FU at least 24 hrs before administration of 9NC or 9AC. In contrast, Bernacki et al. discloses in vitro studies of combination of 9NC and 5FU concurrently or with 5FU administered after 9NC. In particular, Bernacki et al. found that "sequential combination of 9NC or SN-38 followed by 5-FU, 24 hr later appeared to be highly synergistic at high dose-effect levels (i.e., $ID_{90}$), suggesting that sequential drug administration may be more efficacious at high effect level and that the order of drug addition is very important." *See* Abstract. In view of this teaching of the importance of the order of administration and the synergistic effects of sequential combination of 9NC followed by 5-FU, one of ordinary skill in the art would not be motivated to reverse the order of administration of 9NC and 5-FU to arrive at the claimed invention.

According also discussed in the interview, none of the cited references teaches or suggests administering 9NC (or 9AC) at least 1 day after administration of 5FU in a patient with p53 mutation. Rubinfeld neither teaches administering 9NC or 9AC to a cancer patient at least 1

day before or after administration of 5-FU, nor suggests that such a water insoluble campthecin compound should be administered while 5-FU is not present in a pharmaceutically active form in the body. On the other hand, Achterrath merely teaches a combination therapy of a water soluble 5- campthecin derivative CPT-11, fluorouracil (5-FU), and folinic acid (FA). The combination of CPT-11 and 5-FU is administered within a 24-hr time period. Column 5, lines 23-28. Thus, both Rubinfeld and Achterrath fail to teach the claimed sequential therapy which involves administering 9NC or 9AC at least 1 day after the administration of 5-FU.

In view of the failure of the cited references to teach or suggest the claimed sequential therapy, Applicants submit that a prima facie case of obviousness has not been established under 35 U.S.C. §103(a). Withdrawal of this ground of rejection is therefore respectfully requested.

## CONCLUSION

Applicants believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent to issuance. Should the Examiner have any questions, Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

Date: April 19, 2005 By: _____

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